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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/714,195	11/14/2003	Joffre B. Baker	39740-0005A	5745

25213 7590 10/19/2007

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EXAMINER	
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ART UNIT	PAPER NUMBER
1634	

MAIL DATE	DELIVERY MODE
10/19/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/714,195	BAKER ET AL.	
	Examiner	Art Unit	
	Amanda M. Shaw	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 July 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *31,35-38,40-47,51,52,56,57 and 59-61* is/are pending in the application.

4a) Of the above claim(s) *40* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *31,35-38,41-47,51,52,56,57 and 59-61* is/are rejected.

7)☒ Claim(s) *57 and 60* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *21 December 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on July 23, 2007 has been entered.

Claims 31, 35-38, 40-47, 51-52, 56-57, and 59-61 are currently pending. Claims 31, 40-41, 51-52, 56-57, and 59-61 have been amended.

Claim 40 is withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected subject matter, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on May 23, 2006. If is further noted that the rejection of claim 40 on the Office Action Summary Sheets from June 21, 2006 and February 22, 2007 is a typographical error. This claim has never been examined for patentability. The examiner regrets the confusion.

Therefore Claims 31, 35-38, 41-47, 51-52, 56-57, 59-61 will be addressed herein.

Withdrawn Rejections

2. The rejections made under 35 USC 112 2nd paragraph in section 6 of the Office Action of January 22, 2007 is withdrawn in view of amendments made to the claims.

Claim Objections

The following are new objections:

3. Claim 57 is objected to because the claim recites "expression of LAMC2 or GPC3 genes or gene, wherein". The recitation "genes or gene" appears to be an editing error.

Claim 60 is objected to because the claim recites RNA transcripts which have not been elected.

Claim Rejections - 35 USC § 112 1st paragraph

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

New Matter

The following is a new rejection:

5. Claims 31, 35-38, 41-47, 51-52, 56-57, and 59-61 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the

inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

In the instant case the specification does not appear to provide support for the amendment which recites "A method for predicting the likelihood that a human colon cancer patient will respond to treatment with an ErbB1 inhibitor". The specification (page 1) states that the present invention allows a physician to predict whether a patient is likely to respond well to treatment with an EGFR inhibitor. It is noted that in the response filed on July 23, 2007 the Applicants assert that one skilled in the art would know that the EGFR receptor is also referred to as ErbB1. The Applicants further claim that support for this is found in the attached dictionary of Cancer Terms from the National Cancer Institute, however it appears that this attachment is missing from the Applicants response. The Applicants response has been fully considered however it is not convincing. Previously the claims referred drawn to an EGFR inhibitor which is broadly defined in the specification (page 12) as a molecule having the ability to inhibit a biological function of a native epidermal growth factor receptor. The prior art of Riese (BioEssays 1998) teaches that there are at least eight different hormones in the EGF family and there at least four different receptors (ErbB1, ErbB2, ErbB3, and ErbB4) for these hormones. Riese further teaches that a single hormone is capable of binding to multiple receptors and a single receptor can bind to multiple hormones (page 42). Therefore the claims previously encompassed molecules having the ability to inhibit a biological function of either ErbB1, ErbB2, ErbB3, or ErbB4. However now the claims have been limited to molecules having the ability to inhibit the biological function of only

ErbB1. In the instant case the introduction of claim changes which involve narrowing the claims by introducing elements or limitations which are not supported by the as filed disclosure is a violation of the written description requirement. While the specification discloses the genus of EGF receptors the specification does not disclose a single particular species within this genus. Thus the specification does not provide specific support ErbB1 inhibitors. Further the Applicants have stated that they have amended the claims to recite the ErbB1 receptor to clairfy that a specific receptor ErbB1 is meant and not the class of EGFR receptors, thus their own arguments imply that ErbB1 is not equivalent to EGFR.

Enablement

The following rejection has been modified:

6. Claims 31, 35-38, 41-47, 51-52, 56-57, and 59-61 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contain subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The following factors have been considered in formulating this rejection (*In re Wands,* 858F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988): the breadth of the claims, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, the amount of direction or guidance

presented, the presence or absence of working examples of the invention and the quantity of experimentation necessary.

Nature of the Invention

The invention is drawn to a method for predicting the likelihood that a colon cancer patient will respond to treatment with an ErbB1 inhibitor. Claim 31 comprises determining the normalized level of LAMC2 or GPC3 in a sample comprising ErbB1 expressing cancer cells wherein a higher normalized level of LAMC2 transcript is indicative that the patient will show a decreased likelihood of response to treatment with an ErbB1 inhibitor and a higher normalized level of GPC3 transcript is indicative that the patient will show a increased likelihood of response to treatment with and ErbB1 inhibitor. Claim 56 comprises predicting a decreased likelihood of response if the expression level of LAMC2 gene is elevated in said patient and predicting an increased likelihood of response if the expression level of GPC3 gene is elevated in said patient. Claim 57 comprises identifying evidence of differential expression of LAMC2 or GPC3 genes wherein evidence of increased expression of LAMC2 indicates that siad patient will show a decreased likelihood of response to treatment with an ErbB1 inhibitor and evidence of increased expression of GPC3 indicates that said patient will show an increased likelihood of response to treatment with an ErbB1 inhibitor. The invention is in a class of inventions which the CAFC has characterized as 'the unpredictable arts such as chemistry and biology" (Mycolgen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Federal Circuit 2001)). The nature of the invention requires the knowledge

of a reliable association between the levels of LAMC2 or GPC3 in a sample and how a patient will respond to treatment with an ErbB1 inhibitor.

Scope of the Claims:

The claims are extremely broad over the recitation of the phrase "a higher normalized level" because the claims do not set forth what the normalized level is "higher" than, nor do the claims set forth how much higher the level must be to be predictive. Additionally the terms "increased likelihood" and "decreased likelihood" are extremely broad. The standard used to determine whether a likelihood is "increased" or "decreased" is unknown. Also the term "response" is broad because it encompasses any type of response (i.e., remission of cancer, side effects, etc.). Further the term "ErbB1 inhibitor" is broad in that it includes every inhibitor in the class of ErbB1 inhibitors as well as molecules which inhibit ErbB1 indirectly.

Teachings in the Specification and Examples:

The specification never discusses ErbB1 nor ErbB1 inhibitors in particular. However the specification does discuss a broader class of molecules, namely EGFR and EGFR inhibitors. Specifically the specification (page 25) teaches that EGFR is known to be active in several tumor types such as breast, colon, and head and neck cancers. The specification also teaches that several EGFR inhibitors are promising drug candidates for the treatment of EGFR expressing cancers. The specification further teaches the following EGFR inhibitors: (i) Iressa is a small synthetic quinazoline that competitively inhibits the ATP binding site of EGFR and has been in Phase III clinical trials for the treatment of non-small-cell lung carcinoma; (ii) [agr]cyano-

[bgr]methyl-N-[(trifluoromethoxy)phenyl]-propenamide (LFM-A12) has been shown to inhibit the proliferation and invasiveness of EGFR positive human breast cancer cells; (iii) Cetuximab is a monoclonal antibody that blocks the EGFR and EGFR -dependent cell growth that is currently being tested in phase III clinical trials; and (iv) Tarceva™ which has shown promising indications of anti-cancer activity in patients with advanced ovarian cancer, and non-small cell lung and head and neck carcinomas. The specification does not disclose any ErbB1 inhibitors or teach that ErbB1 inhibitors are equivalent to EGFR inhibitors. Further the specification does not teach if the EGFR inhibitors act equally against al types of EGFR.

The specification (page 3)teaches that the present invention is based on findings of Phase II clinical studies of gene expression in tissue samples obtained from EGFR expressing colon cancer patients who responded well or did not respond to treatment with EGFR inhibitors. The specification further teaches (page 28) that twenty-three colon adenocarcinoma patients in all were studied using a 192-gene assay. Both pathological and clinical responses were evaluated. Following treatment with a single unspecified EGFR inhibitor, three patients were determined to have had a partial response, five to have stable disease, and fifteen to have progressive disease. Table 3 shows the results obtained using the partial response criterion. Both GPC3 and LAMC2 where found to be overexpressed. Specifically GPC3 had a positive response and a p value of 0.0097, while LAMC2 had a negative response and a p value of 0.0357. Here the term "negative" indicates that greater expression of the gene decreased likelihood of response to treatment with EGFR inhibitor, and "positive" indicates that increased

expression of the gene increased likelihood of response to EGFR inhibitor (page 28). The results from analysis of colon cancer patient data using clinical benefit criteria are shown in Table 4. Specifically GPC3 had a positive response and a p value of 0.0025 and there is no data provided for LAMC2.

In the instant case the specification does not teach which EGFR inhibitors were used in the study. Therefore it is unclear if the claimed method can be used to predict the likelihood that a human colon cancer patient will respond to treatment with any ErbB1 inhibitor. Further the specification does not define what would be considered as an "increased likelihood of response" or a "decreased likelihood of response." The results presented show that after treatment three patients were determined to have had a partial response, five to have stable disease, and fifteen to have progressive disease. In the instant case it is unclear if the five patients with stable disease are considered responders since their disease did not worsen or are they considered non-responders since they did not show a partial response. Further it is unclear what is encompassed by a partial response. Additionally the specification does not teach the level of expression of LAMC2 and GPC3 in the cancer patients or the normalized level of LAMC2 and GPC3 as to provide guidance as to how a "higher normalized level" can be determined.

State of the Art and the Unpredictability of the Art:

The state of the art at the time of Applicant's filing was underdeveloped with regard to the use of RNA transcripts such as LAMC2 transcripts and GPC3 transcripts

to predict the likelihood that a patient with an ErbB1 colon cancer will respond to treatment with an ErbB1 inhibitor.

The unpredictability of correlating a gene expression level with an individual's response to treatment is taught in the post filing date art by Evans (Nature 2004). Evans teaches that differences in DNA sequences that alter the expression or function of proteins that are targeted by drugs can contribute significantly to variation in the responses of individuals (Abstract). Evans teaches that most drug effects and treatment outcomes are determined by an interplay of multiple genes (Page 464 Column 2). Evans further teaches that although single gene defects can have a strong effect on their substrates, most of the phenotypic variability in drug response remains unexplained despite numerous efforts to interrogate candidate genes and pathways (Page 465, Column 1). Additionally Lee (The Oncologist 2005) teaches that while genes likely contribute to the observed variability in cancer treatment outcome, there are several other variables that have been found to be associated with drug responses such as age, gender, diet, drug-drug interactions (Abstract).

In fact the unpredictability of correlating gene expression level to any phenotypic quality is taught in the art of Wu (2001). Wu teaches that gene expression data, such as microarray data, must be interpreted in the context of other biological knowledge, involving various types of post genomics informatics, including gene networks, gene pathways, and gene ontologies (page 53). The reference indicates that many factors may be influential to the outcome of data analysis, and teaches that expression data can be interpreted in many ways. The conclusions that can be drawn from a given set of

data depend heavily on the particular choice of data analysis. Much of the data analysis depends on such low-level considerations as normalization and such basic assumptions as normality (page 63). The art of Newton et al (2001) further teaches the difficulty in applying gene expression results. Newton et al. teaches that a basic statistical problem is determining when the measured differential expression is likely to reflect a real biological shift in gene expression, and replication of data is critical to validation (p.38, third full paragraph). There is no replication of data in the instant specification. Additionally, post-filing art reveals that most gene association studies are hard to replicate. Lucentini (The Scientist) teaches that it is strikingly common for follow-up studies to find gene- disease associations wrong (page 2). Lucentini teaches that two recent studies found that typically when a finding is first published linking a given gene to a disease there is only roughly a one-third chance that the study will reliably confirm the finding (page 2). Lucentini teaches that bigger sample sizes and more family-based studies, along with revised statistical methods should be included in the gene association studies (page 3).

The claims of the instant application also require a step of determining a "higher normalized level". However the specification is silent as to how much higher the expression needs to be, nor what to compare the normalized level to in order to predict a patient's response to an ErbB1 inhibitor. Since the claims encompass any level of altered gene expression, it is relevant to point out that the art of Cheung et al (2003) teaches that there is natural variation in gene expression among different individuals. The reference teaches an assessment of natural variation of gene expression in

lymphoblastoid cells in humans, and analyzes the variation of expression data among individuals and within individuals (replicates) (p.422, last paragraph; Fig 1). The data indicates that, for example, expression of ACTG2 in 35 individuals varied by a factor of 17; and that in expression of the 40 genes with the highest variance ratios, the highest and lowest values differed by a factor of 2.4 or greater (Fig 3). It is thus unpredictable as to whether or not any level of altered gene expression is predictive of a response.

Further the art of identifying if every ErbB1 inhibitor will be less effective in patients with increased LAMC2 levels and the art of identifying if every ErbB1 inhibitor will be more effective in patients with increased GPC3 levels or gene product levels is highly unpredictable. The genus of inhibitor drugs is expected to be very large. For example the post filing date art of Giaccone teach six EGFR inhibitors (Iressa, Tarceva, lapatinib, cenertinib, ZD6474, and AEE788). Giaccone additionally teaches that each of these drugs has a different mechanism in which it acts on EGFR inhibitor. For example Iressa and Tarceva inhibit the tyrosine kinase of EGFR by competing with ATP for the ATP binding site, lapatinib and canertinib have activity on more members of the ErbB family, and ZD6474 and AEE788 inhibit the vascular endothelial factor receptor in addition to EGFR. Thus it is unpredictable as to whether the results obtained for colon cancer using whichever EGFR inhibitor the inventor used could be extrapolated to other EGFR inhibitors because each inhibitor works by a different mechanism.

Quantity of Experimentation:

The specification asserts patients who had "higher normalized levels" of LAMC2 were less likely to respond to a treatment with an EGFR inhibitor. The specification

asserts patients who had "higher normalized levels" of GPC3 were more likely to respond to a treatment with an EGFR inhibitor. However the specification does not teach how much of a difference between the observed normalized expression level and the undefined comparison standard would be necessary to draw the conclusions set forth in the claims. Further the specification does not teach which EGFR inhibitors were used to test this hypothesis. To answer these questions one would have to conduct extensive experimentation. For example, such experimentation may involve treating patients with different types of EFGR inhibitors and conducting multiple gene expression assays to determine the expression levels of LAMC2 and GPC3. Such random, trial by error experimentation is considered to be undue. The specification has provided only an invitation to experiment.

Conclusions:

Case law has established that '(t)o be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation.'" *In re Wright* 990 F.2d 1557, 1561. *In re Fisher,* 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) it was determined that '(t)he scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art". The amount of guidance needed to enable the invention is related to the amount of knowledge in the art as well as the predictability in the art. Furthermore, the Court in *Genetech Inc. v Novo Nordisk* 42 USPQ2d 1001 held that '(I)t is the specification, not the knowledge of

one skilled in the art that must supply the novel aspects of the invention in order to constitute adequate enablement".

The claims are drawn to a method for predicting the likelihood that a colon cancer patient will respond to treatment with an ErbB1 inhibitor by determining the normalized level of LAMC2 or GPC3 in a sample. As discussed above, whether an association exists between increased levels of LAMC2 and GPC3 and the response to ErbB1 inhibitors is highly unpredictably. In the instant case the specification has not taught a reliable method of associating increased levels of LAMC2 and GPC3 and the response to ErbB1 inhibitors. Accordingly, although the level of skill in the art of molecular biology is high, given the lack of disclosure in the specification and in the prior art and the unpredictability of the art, it would require undue experimentation for one of skill in the art to make and use the claimed invention.

Claim Rejections - 35 USC § 112 2nd paragraph

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 31, 35-38, 41-47, 51-52, 56-57, and 59-61 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 31, 35-38, 41-47, 51-52, and 59-61 are indefinite because the claims do not clearly set forth a step of predicting the likelihood that a human colon cancer patient will respond to treatment with an ErbB1 inhibitor. The claims do not recide a clear

nexus between the preamble and the last step of the method because determining the normalized level of predictive RNA transcripts in a sample is not equivalent to predicting the likelihood that a human colon cancer patient will respond to treatment with an ErbB1 inhibitor.

Claims 31, 35-38, 41-47, 51-52, and 59-61 are indefinite over the recitation of the phrase "higher normalized level". The term "higher" is a relative term which is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

Claims 31, 35-38, 41-47, 51-52, 56-57, and 59-61 are indefinite over the recitation of the phrase "decreased likelihood". The term "decreased" is a relative term which is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

Claims 31, 35-38, 41-47, 51-52, 56-57, and 59-61 are indefinite over the recitation of the phrase "increased likelihood". The term "increased" is a relative term which is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

Claim 56 is indefinite over the recitation of the phrase "expression level of LAMC2 gene is elevated". The term "elevated" is a relative term which is not defined by the claim, the specification does not provide a standard for ascertaining the requisite

degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

Claim 57 is indefinite because the claims do not clearly set forth a step of predicting the likelihood that a human colon cancer patient will respond to treatment with an ErbB1 inhibitor. The claims do not recide a clear nexus between the preamble and the last step of the method because identifying evidence of differential expression is not equivalent to predicting the likelihood that a human colon cancer patient will respond to treatment with an ErbB1 inhibitor.

Claim Rejections - 35 USC § 102

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 31, 35-37, and 57 are rejected under 35 U.S.C. 102(b) as being anticipated by Hlubek (Cancer Research 11/15/2001) as evidenced by Salomon (Critical Reviews in Oncology/Hematology 1995).

Regarding Claim 31 Hlubek teaches a method comprising determining the expression levels of LAMC2 in cells obtained from patients with colorectal adenocarcinomas (Abstract). Hlubek does not specifically teach that the patients had ErbB1 expressing cancer cells, however Salomon teaches that collectively a total of 599 colon tumors have been examined in 12 separate studies and ~25-77% of the colon

cancer patients have ErbB1 expressing cancer cells (Page 196, column 2), therefore in a population of 45 cases, ~11 to 35 of those cases would express ErbB1. Thus Hlubek teaches a method of determining expression of the LAMC2 transcript in a sample from a patient with an ErbB1 expressing colon cancer. In the instant case the method of claim 31 has a single method step of determining the level of a RNA transcript. The "wherein clause" does not appear to effect the method step therefore has not been accorded any patentable weight.

Regarding Claim 35 Hlubek teaches that the sample is a tissue sample (Page 8089, under heading "Tissue Specimens").

Regarding Claim 36 Hlubek teaches that the tissue samples were formalin fixed and paraffin embedded (Page 8089, under heading "Tissue Specimens").

Regarding Claim 37 Hlubek teaches that the tissue samples were from patients who underwent surgery. This is being interpreted as a biopsy (Page 8089, under heading "Tissue Specimens").

Regarding Claim 57 Hlubek teaches a method comprising determining the expression levels of LAMC2 in cells obtained from patients with colorectal adenocarcinomas (Abstract). Hlubek does not specifically teach that the patients had ErbB1 expressing cancer cells, however Salomon teaches that collectively a total of 599 colon tumors have been examined in 12 separate studies and ~25-77% of the colon cancer patients have ErbB1 expressing cancer cells (Page 196, column 2), therefore in a population of 45 cases, ~11 to 35 of those cases would express ErbB1. Thus Hlubek teaches a method of identifying evidence of differential expression of LAMC2.

Claim Rejections - 35 USC § 103

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

10. Claims 41-47, 52, and 59-60 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hlubek (Cancer Research 11/15/2001) as evidenced by Salomon (Critical Reviews in Oncology/Hematology 1995) and in further view of Bao (US 6251601 Issued 2001).

The teachings of Hlubek as evidenced by Salomon are presented above.

Hlubek does not teach a method wherein the expression of the LAMC2 transcript is determined using a microarray.

However Bao teaches that expression can be determined using an array of nucleic acid target elements attached to a solid support (abstract). Bao teaches that the nucleic acid target elements can be cDNAs (Column 6, lines 32-35). Bao teaches that the target elements can be between 100 bp and 5000 bp (column 8, lines 45-49). Bao also teaches that the target elements can be oligomers ranging between 20 to 80 base pairs (Column 8, lines 27-30). Bao teaches that the array can contains about 100 to about 10,000 target sequences (Bao Column 9, lines 44-46). Bao teaches that any suitable substrate can be used including glass (Column 11, lines 37-40). Bao further teaches using a kit such as the QIAamp tissue kit for DNA extraction and isolation (column 12, l lines 13-16). Bao also teaches that the array can have nucleic acid analogs which are being interpreted as modified nucleic acids (column 7, lines 35-37).

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Hlubek by performing the expression analysis on a microarray as suggested by Bao. The microarray of Bao combines the capability of assessment of a large number of nucleic acids provided by microarray test formats to assess simultaneously both gene expression and genomic abnormalities in the same sample (Column 7, lines 9-22). Thus it would have been obvious to an ordinary artisan to use such an array to study colon cancer expression for the benefit of simultaneously determining gene expression and genomic abnormalities.

11. Claim 60 is rejected under 35 U.S.C. 103(a) as being unpatentable over Hlubek (Cancer Research 11/15/2001) as evidenced by Salomon (Critical Reviews in Oncology/Hematology 1995) and in further view of Chun (J Korean Med Sci 2000).

The teachings of Hlubek as evidenced by Salomon are presented above.

The combined references do not teach a method wherein the expression of CD44v6 is also determined.

However teaches that they determined the expression level of CD44v6 in colorectal tumors (Abstract).

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Hlubek by assaying the expression level of CD44v6 in colorectal tumors as suggested by Chun especially since Chun teaches that CD44v6 can be a molecular marker for colorectal cancer and its mcirometastasis.

12. Claim 61 is rejected under 35 U.S.C. 103(a) as being unpatentable over Hlubek (Cancer Research 11/15/2001) as evidenced by Salomon (Critical Reviews in Oncology/Hematology 1995) and in further view of Filmus (Glycobiology 2001).

The teachings of Hlubek as evidenced by Salomon are presented above.

The combined references do not teach a method wherein both LAMC2 and GPC3 are assayed.

However Filmus teaches that they determined the expression level of GPC3 in colorectal tumors (Page 21 R, second column).

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Hlubek by assaying the expression level of GPC3 in colorectal tumors as suggested by Filmus especially since Filmus teaches that a significant proportion of colorectal tumors express GPC3 and normal colon does not express GPC3 (Page 21 R, second column). Therefore GPC3 may be a good marker for colon cancer.

Response to Amendment

13. In the reply filed July 23, 2007 the Applicants have once again traversed the requirement to elect a single gene or combination of genes with respect to claim 60. The applicants argue that since claim 60 depends from claim 31, if claim 31 is found allowable then claim 60 must be allowable as well. The Applicants also argue that there is not an undue burden on the examiner for this. This argument has been fully considered but is not persuasive. First of all the fact that claim 60 depends from claim 31 does not necessarily render claim 60 allowable if claim 31 is allowable. Claim 60 would be free of the art and subject to possible rejoinder, however claim 60 would also have been considered with respect to 35 USC 101 and 112 issues. It is further noted that the 47 different genes encompassed by claim 60, and the various combinations thereof also encompassed by the claims, differ in sequence and structure from one another, and possess different functional properties and characteristics. In accordance with the policy set forth in 1316 OG 122 (27 March 2007), claims directed to polynucleotide molecules or method of using polynucleotide molecules are considered

for independence, relatedness, distinction, and burden as for claims to any other type of molecule. Accordingly, the genes and combinations of genes are thus deemed to constitute independent and distinct inventions within the meaning of 35 U.S.C. 121. It is further noted that in the Office Action of 12/23/2005 the Applicants were instructed to elect **one gene or a combination of genes** in Claim 60. However in the reply filed on 5/23/2006 the Applicants only elected to have CD44v6 considered. Rejoinder of additional genes in claim 60 will be considered upon a finding of allowable subject matter.

With regard to the enablement rejection the Applicants argue that they have shown that the prognostic information obtained from the over expression of LAC2 or GPC3 RNA transcripts are applicable to any EGFR (ErbB1) inhibitor (Page 9). Applicants have previously filed a declaration by Joffre B. Baker, Ph.D., one of the inventors, wherein Dr. Baker states that the patients were treated with an EGFR inhibitor selected from the group erlotinib, gefitinib, cytoximab, EMB72000, and AEE788. He further says that all the results presented in Example 2 and Tables 3 and 4 were the result of treatment with a variety of different EGFR inhibitors. Therefore it is his belief that the prognostic information obtained by over expression of the LAMC2 or GPC3 is applicable to treatment with the class of drugs called EGFR inhibitors which inhibit a biological function of a native EGFR. Both the Applicants arguments and Dr. Baker's declaration have been fully considered. Again the specification does not teach a method which uses the inhibitors disclosed in the declaration. Furthermore the specification does not even mention all of these inhibitors. Additionally it is pointed out

that there is no specific data provided in the declaration for each drug that was tested. The specification teaches that only three patients were found to have had a partial response yet the Applicants have not provided any information as to which drug these patients received, if these patients were all on the same drug or different drugs, or the LAMC2/GPC3 expression levels of these patients. Therefore it is impossible for one to conclude that these patients had an increased response due to their LAMC2/GPC3 expression levels based on the amount of information that has been provided by the Applicants. The Applicants also argue on page 11 that inhibitors will inhibit the action of the ErbB1 dimer in a number of different ways and if the ErbB1 dimers is inhibited than its action on the various cellular pathways downstream of the ErbB1 dimer will also be inhibited. The Applicant claim that since they have shown that the LAMC2 and GPC3 genes are prognostic indicators for the likelihood of pateint response to treatment with an EGFR inhibitor, nothing further is required. This is not persuassive because the Applicants have not demonstrated that the LAMC2 and GPC3 genes are prognostic indicators for the likelihood of pateint response to treatment with any EGFR inhibitor. As discussed above the class of EGFR inhibitors is quite large and each inhibitor works by a different mode of action.

Additonally the Applicants are reminded that there are other remaining issues with regard to enablement. There is still a lack of critical guidance in the specification and claims. For example the specification does not define what would be considered as an "increased likelihood of response" or a "decreased likelihood of response." Further it is unclear what is encompassed by a partial response. Additionally the specification

does not teach the level of expression of LAMC2 and GPC3 in the cancer patients or the normalized level of LAMC2 and GPC3 as to provide guidance as to how a "higher normalized level" can be determined.

The portion of the enablement rejection stating that the term "corresponding gene products" is broad is withdrawn in view of amendments made to the claims.

The portion of the enablement rejection stating that the specification does not teach that LAMC2 and GPC3 are overexpressed in colon cancer is withdrawn in view of the Applicants arguments.

The portion of the enablement rejection stating that the specification does not provide an example for determining the normalized level of a representative number of corresponding gene products of LAMC2 or GPC3 is withdrawn in view of Applicants amendments.

Conclusion

10. No Claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Amanda M. Shaw whose telephone number is (571) 272-8668. The examiner can normally be reached on Mon-Fri 7:30 TO 4:30. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached at 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Amanda M. Shaw
Examiner
Art Unit 1634

JULIET C. SWITZER
PRIMARY EXAMINER